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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/589,288	06/08/00	YU G	PF343P3C5

022195
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HM12/1106

EXAMINER	
PRASAD,S	
ART UNIT	PAPER NUMBER
1646	8

DATE MAILED: 11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/589,288	YU ET AL.	
	Examiner	Art Unit	
	Sarada C Prasad	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,17,19 and 26-164* is/are pending in the application.

4a) Of the above claim(s) *1,17 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-164* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

1. Applicant's election with traverse of Group IV (claims 26-164) in Paper No. 6 (8/17/01) is acknowledged. Upon entry of the amendment in Paper No. 6 (8/20/01), original claims 2-26, 18, and 20-25 have been cancelled, and new claims 26-164 have been added. Currently, claims 1,17, 19, and 26-274 are pending.

The traversal is on the ground(s) that a search of the polynucleotide claims would clearly provide useful information for the polypeptide claims and a search of the polypeptide claims, as a matter of routine, would include a search for antibodies, and hence restriction of original claims 1-25 to Groups I, II, III is not proper. This is not found persuasive because the inventions of Groups I, II and III, directed to polynucleotide, polypeptide, and antibodies are distinct as noted in the last Office Action, and as shown by the distinctness described therein. Applicant's attention is directed to MPEP 806.05. Contrary to applicants' assertion that any search of the prior art in regard to Group I would reveal whether any prior art exists as to the other inventions of Groups II and III, the search is in fact directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a focussed search of relevant literature in many different areas of subject matter. Furthermore, divergent classification of the three Groups of inventions I-III has been an additional criterion for the restriction of the claims 1-26 into three distinct inventions. Each of these inventions would require non-cohesive classification searches posing an undue burden for the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Currently, original claims 1,17, and 19 have been withdrawn as being non-elected, and new claims 26-164 are under consideration.

Specification

2a. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

2b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. A suggested title would be 'Methods of treatment using antibodies to neutrokine-α'.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 26-164 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Issues that are addressed in this rejection:

There are two major aspects of total lack of enablement addressed in this rejection: (a) treatment of immune system disease, or disorder, or autoimmune diseases, or disorder, or immunodeficiency using antibodies that specifically bind to 'full length neutrokine-α of SEQ ID No. 2; and (b) use of antibodies that specifically bind to full length polypeptide of SEQ ID No. 2 or fragments, derivatives, portions or fusion peptides, or N-, C-, N- and C- terminal deletion mutants of neutrokine-α of SEQ ID No. 2 for any treatment of immune system disease, or disorder, or autoimmune diseases, or disorder, or immunodeficiency.

What does the specification set forth:

The specification sets forth general methods for preparation of (a) epitope bearing peptides (starting at 2nd para on page 113, until 1st para on page117) that constitute various lengths of antigenic regions covering the entire 1-285 amino acid long sequence of SEQ ID NO.2; (b) antibodies to these various derivatives of SEQ ID No. 2 for use as antagonists (page 24, 3rd para, lines 5-6); and (c) various antibody derivatives or portions thereof containing the antibody binding site (Fab fragments), or antibodies amenable to use in human beings (chimeric, humanized, fusion proteins with detection tags) in pages 228-261. However, very few specific examples of such contemplated 'antibodies directed to specific regions of SEQ ID NO. 2' are disclosed (Examples 9 and 10, pages 427-433). In particular, the specification discloses screening of 729 hybridomas with the result that 23 of them were positive, including 16 IgM and 7 IgG producers (page 431, 4th para, lines 5-end). Instant disclosure also states that preliminary experiments demonstrated that the antibody neutralized the binding of neutrokine-α to its receptor on B lymphoid cells (page 432, 5th para, first 2 lines), while one of the antibodies binds

to both soluble and membrane bound forms of neutrokine-α (page 433, first two lines). These were the only two real world antibodies shown though not well characterized.

The specification is not enabled for a method of treating an immune system disease or disorder, or autoimmune disease or disorder, or immunodeficiency comprising administering to an individual, a therapeutically effective amount of an antibody or a portion thereof that specifically binds to a protein consisting of

(i) an amino acid sequence 1-285 of SEQ ID No. 2, or amino acid residues 72-285 of SEQ ID No.2, or amino acid residues 134-285 of SEQ ID No.2;

(ii) an amino acid sequence of amino acid residues n-285 of SEQ ID No.2, where n is an integer in the range of 2-190; or amino acids residues 1-m of SEQ ID No.2 where m is an integer in the range of 274-284;

(iii) an amino acid sequence of an amino terminal deletion protein mutant of the full length protein encoded by the cDNA contained in ATCC deposit number 97768, wherein said amino terminal deletion protein mutant excludes up to 190 residues from the amino terminus of said full length protein encoded by the cDNA contained in ATCC deposit number 97768;

(iv) an amino acid sequence of a carboxy terminal deletion protein mutant of the full length protein encoded by the cDNA contained in ATCC deposit number 97768, wherein said carboxy terminal deletion mutant excludes up to 11 amino acid residues from the carboxy terminus of said full length protein encoded by the cDNA contained in ATCC deposit number 97768;

(v) the amino acid sequence of an amino and carboxy terminal deletion protein mutant of the full length protein encoded by the cDNA contained in ATCC deposit number 97768, wherein

said amino and carboxy terminal deletion protein mutant excludes up to 190 amino acids from the amino terminus and up to 11 residues from the carboxy terminus of said full length protein encoded by the cDNA contained in ATCC deposit number 97768, wherein the peptide sequence modulates lymphocyte proliferation;

the specification is also not enabled for a method of inhibiting leukocyte proliferation or activation comprising administering to an individual, a therapeutically effective amount of an antibody or portion thereof that specifically binds a protein consisting of

(vi) an amino acid sequence of amino acid residues n-285 of SEQ ID No.2, where n is an integer in the range of 2-190; or amino acids residues 1-m of SEQ ID No.2 where m is an integer in the range of 274-284; or amino acid residues 134-285 of SEQ ID No.2.

Analyses of why the instant claims lack enablement:

Diversity of diseases to be treated:

The specification is not enabled for claims reciting treatment of immune system disease or disorder or autoimmune disease or disorder or immunodeficiency with the instant remedy of administering effective amount of antibodies to neutrokine-α . There is no guidance for one of skill in the art for selection of patient population for treatment, and what are the particular symptoms to alleviate other than inhibit B-lymphocyte proliferation. The limited guidance provided is not complete with the only one response (neutralization of neutrokine biding to its receptor) observed to be affected by the instant antibodies. State of the art dictates that for treatment of any particular disease the expected outcome is relief of symptoms, which has not been provided in the specification. It is essential to have guidance for the diseases to be treated because the expected relief of symptoms depends on the nature of disease symptoms.

Furthermore, recitation of treatment of '....disorder....' includes any combination of symptoms that might or might not have been classified as belonging to any one disease in particular. Therefore, it is not feasible for one of skill in the art to treat unnamed immune system disease, or autoimmune disease, or disorder, or immunodeficiency as recited in the instant claims.

Diversity of the contemplated antibodies for use in the treatment of the diverse diseases:

Instant specification fails to provide what is the specificity of the numerous proposed antibodies to the contemplated antigenic/epitopic regions. It is not feasible for a skilled artisan to state that any one of such antibodies specifically binds to which of the 1-285 residues of SEQ ID NO.2 unless each of these antibodies is characterized. Example X shows that there is one such antibody that has been disclosed in the instant specification, 15C10 (page 432, 4th and 5th paragraphs). However, guidance is not provided as to what was the immunogen/antigen that resulted in generation of this particular antibody, what was the immunogen/antigen that resulted in generation of this particular antibody, what was the neutrokine-α response that was inhibited, other than mention that this antibody was able to neutralize the binding of neutrokine-α to its receptor. In spite of the numerous contemplated epitope bearing regions of SEQ ID No. 2 and the corresponding antibodies, the specification fails to provide information on the comparison of such antibodies to full length polypeptide to those directed to portions of SEQ ID NO. 2 for responses such as (a) inhibition of B-lymphocyte proliferation, (b) neutralization of ligand receptor interaction, or (c) a table of the immunogens used and the titers of the antibodies generated in binding to the full length polypeptide or the said fragments.

State of the art dictates that inhibition of the transduction of the signal that is subsequent to ligand receptor interaction as a result of antibody interference is essential for the claimed effectiveness, and functionality of the claimed antibodies directed to various regions of neutrokine-α in order for them to be useful for therapy of immune system related diseases. It is clear from the instant specification that the myriad of claimed antibody specificities to SEQ ID No. 2 are hypothetical. Additionally, the numerous possible applications of these antibodies to therapeutic end, contemplated in the specification, are largely dependent upon the structural similarity of neutrokine-α to TNF like ligands, and the diseases that several TNF-ligands are associated with. In fact, the instant contemplated antibodies to SEQ ID No. 2 appear to have been set up as a corollary to the TNF ligand interaction with its receptor and the diseases thereof.

In order to fulfill the enablememt requirement, the application has to be complete at the time of submission and not later. Having an antibody is not equivalent to being able to treat the disease or disorder that the particular antigen relates to. In fact, with the state of the art techniques describing antibodies useful for therapeutic purposes would require extensive in vitro and in vivo characterization of antibody specificity as well as testing for the alleviation of symptoms of the disease or disorder being considered for therapy; and finally such attempts would have to go through clinical trials. The instant antibodies to SEQ ID No. 2 have not been shown to modulate symptoms of any of the several diseases that the claims encompass. Also, the antibodies of the instant invention have not been disclosed to inhibit any of the responses of B-lymphocytes that the neutrokine-α polypeptide would elicit. The specification just provided the methods of assays if such antibodies were generated and characterized. Therefore, it is evident

from the instant specification that the Application is not enabled for the instant claims. It appears that the Applicants are asking for a license to perform further experimentation.

See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Given the breadth of claims reciting antibodies to fragments, derivatives, deletion mutants of SEQ ID No. 2 that can be used for the treatment of immune system diseases, in light of the predictability of the art that antibodies to all epitope bearing regions are not useful for the treatment of all the diseases that the antigen is related to, as determined by the lack of working examples showing that the envisioned antibodies to the various epitope berating regions of SEQ ID No. 2 do have the expected specificity and utility for therapeutic purposes, state of the art suggesting how guidance is needed for a skilled artisan for use of each and every specific antibody for treatment of specific disorders, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 27-38, 40-52, 54-63, 75-84, 86-91, 93-100, 102-110, 112-117, 119-130, 132-147, 149-157, 159-164 are rejected insofar as they depend on claims 26, 39, 53, 64, 74, 85, 92, 101, 111, 118, 131, 148, 158.

Conclusion

4. No claims are allowed.

Prior art cited: U.S. Patent No. 6,297,367 (Oct 2001) (WO 99/33980 (12/30/1997).

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday - Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
November 1, 2001